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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/297,877	06/28/1999	VIRGINIA M.-Y. LEE	PENN-0583	1398

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/297,877	LEE ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 4 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 4 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Prosecution Application

The Request for Continued Examination (RCE) filed on 09 February 2004 under 37 CFR 1.114 based on parent Application No. 09/297,877 is acceptable and an RCE has been established. An action on the RCE follows.

Claim 4 is under consideration in the instant application.

Claim Rejections - 35 USC § 112

1. Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth at pg 2-7 of the Office Action of 16 June 2003 and at pg 3-6 of the Office Action of 06 November 2002.

Specifically, claim 4 recites a method of inhibiting the processing of amyloid precursor protein into amyloid β peptides found in neuritic plaques and vascular deposits that accumulate in the brains of patients with Alzheimer's disease comprising administering to a patient an agent which decreases processing of amyloid precursor protein into amyloid β peptides wherein said agent is identified by (i) contacting NTN2 cells with the agent and (ii) measuring levels of amyloid β peptides formed in the endoplasmic reticulum (ER) of the cells.

The specification teaches that NT2N neurons are metabolically labeled with [^{35}S]methionine in the presence or absence of Brefeldin A (BFA) (pg 9, lines 2-4). The specification discloses that in the absence of BFA, full length APP, APPβ, and Aβ are recovered from cell lysates while APPα, APPβ, and Aβ are detected in the media of the NT2N neurons.

The specification also teaches that in the presence of BFA, full length APP, APPβ, and Aβ are recovered from NT2N cell lysates, but the secretion of APPα, APPβ, and Aβ into the medium is completely abolished in the presence of BFA (pg 9, lines 8-13). Furthermore, the specification teaches that an ER-retention signal is placed in APP695 ($APP695_{\Delta KK}$) wherein this lysine motif signal is sufficient to retain heterologous transmembrane proteins in the ER and intermediate compartment (pg 9, lines 33-37). BFA treatment of NT2N neurons expressing $APP695_{\Delta KK}$, blocks surface expression of APP695 while $APP695_{\Delta KK}$ does not acquire resistance to endoglycosidase H digestion, indicating that $APP695_{\Delta KK}$ is retained in the ER (pg 10, lines 13-18). The specification also discloses that SFV-infected NT2N cells are metabolically labeled overnight and Aβ is immunoprecipitated from the medium and cell lysate. The specification teaches that ER retention of APP by the KK retention signal blocks Aβ secretion, but fails to block all intracellular Aβ biosynthesis. The specification teaches that as with Brefeldin A (BFA) treatment, cells expressing $APP695_{\Delta KK}$ produce 40% of the total intracellular Aβ generated from APP695. This reduction is because of the loss of Aβ40. Aβ42 levels are not effected (pg 10, lines 22-33).

However, the specification of the instant application does not teach any methods or working examples wherein a patient is administered an agent which decreases processing of amyloid precursor protein into amyloid β peptides found in neuritic plaques and vascular deposits that accumulate in brains of patients with Alzheimer's disease. Since there is inadequate guidance in the specification, the skilled artisan must use the current invention as a starting point for further experimentation. Furthermore, the present invention is unpredictable and complex wherein the claimed method may not necessarily inhibit the processing of amyloid

precursor protein into amyloid β plaques *in vivo*. The skilled artisan must resort to trial and error experimentation to determine the optimal dosage, duration, and mode of administration of all possible agents. Such trial and error experimentation is considered undue. Additionally, since the specification provides no guidance regarding what sort of agents should be screened for inhibiting the processing of amyloid precursor protein, the skilled artisan must resort to trial and error experimentation to determine which class of compounds might yield one with the desired activity. Such trial and error experimentation is considered undue.

Furthermore, Alzheimer's disease is recalcitrant to treatment and relevant literature reports that there is no cure for Alzheimer's disease and that only recently have therapeutic *strategies* emerged (Brinton et al. Pharmaceutical Res 15(3): 386-398, 1998; pg 386, ¶ 1). For example, Brinton et al. indicates cholinergic pharmaceuticals only modestly improve cognitive function, have short-lived effects, and are in the early stage of development (Brinton et al., pg 393, col 2, ¶ 4 through pg 394). Brinton et al. also mentions that unlike animal studies with NGF, human trials have not been successful (pg 394, col 1). Additionally, Roses (Lancet 355: 1358-1361, 2000) discloses that "if an effective treatment were to be developed for a common form of the illness, it might not work for all patients, especially those with rare mutational forms of Alzheimer's disease. Conversely, a treatment developed for a specific mutation may have no effect in common Alzheimer's phenotypes" (pg 1358, bottom of col 1 through top of col 2). Roses also states that a patient's response to a drug may depend on other factors than the alleles the individual carries, such as drug distribution, drug absorption, drug concentration at the target site, and drug metabolism and elimination (pg 1358, col 2, ¶ 1).

Furthermore, Applicant's arguments (17 September 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that the Examiner has misinterpreted claim 4 and that claim 4 is directed to a method of inhibiting a biological endpoint (i.e., processing of amyloid precursor protein into amyloid beta peptides) which is asociated with one sign (i.e, neuritic plaques and vascular deposits) of Alzheimer's disease and not a method of preventing or treating Alzheimer's disease. It is noted to Applicant that the Examiner has not misinterpreted claim 4 as prevention or treatment of Alzheimer's disease (AD). Claim 4 does not specifically recite the prevention or treatment of Alzheimer's disease, but rather, the inhibition of the processing of amyloid precursor protein into amyloid β peptides. However, the Examiner has interpreted one of the steps of claim 4 as administering an agent to AD patients (lines 1-7).

(ii) Applicant asserts that an *in vitro* model example which correlates with the disclosed or claimed method of invention has been provided. Applicant contends that the assertion that the claimed invention is useful in inhibiting a sign of a disease in a patient would be considered credible and predictable by a person of ordinary skill in the art on the basis of using the NTN2 cells to identify an agent which modulates the levels of amyloid beta peptides formed in the ER of said cells. Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, as discussed in previous Office Actions, the specification of the instant application outlines a prophetic procedure for treating Alzheimer's disease with an agent that inhibits the processing of amyloid precursor protein into amyloid β peptides (pg 4, lines 29-37 through pg 5, lines 1-9). However, this disclosed suggestion and the *in vitro* experiments with

NT2N cells (pg 9-10) is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily inhibit the processing of amyloid precursor protein into amyloid β peptides in patients with Alzheimer's disease by administration of an agent that decreases said processing. Although part of the claimed method utilizes routine agent identification techniques, the results of the method are unpredictable and complex when combined with the step of administering the agent identified to a patient with Alzheimer's disease. Also, although the NT2N model system is a predictable system used to study APP processing in neurons, it is not an art recognized model system for Alzheimer's disease. Therefore, one skilled in the art would not predict from the guidance in the specification that an agent that decreases amyloid precursor protein processing in the NT2N model system would necessarily decrease amyloid precursor protein processing in a patient.

Furthermore, the skilled artisan must resort to trial and error experimentation to determine the optimal dosage, duration, and mode of administration of all possible agents. Since the specification provides no guidance regarding what sort of agents should be screened for inhibiting the processing of amyloid precursor protein, the skilled artisan must resort to trial and

error experimentation to determine which class of compounds might yield one with the desired activity. Such trial and error experimentation is considered undue.

(iii) Applicant also asserts that as the secretase enzymes are proteases, the skilled artisan would know of, e.g. protease inhibitors or classes of other compounds which may be identified by contacting NT2N cells with such classes of agents and measuring levels of amyloid beta peptides formed in the ER of said cells. Applicant also indicates that the courts have recognized that while a specification may lack examples of specific dosages, the application is considered enabled to one skilled in the art if the agent has certain pharmacological properties (*In re Bundy*, 642 F.2d 430, 434, 209 USPQ 48, 51-52 (CCPA 1981). Applicant's arguments have been fully considered but are not found to be persuasive. The fact pattern of the instant application is not inconsistent with *In re Bundy*, 642 F.2d 430, 434, 209 USPQ 48, 51-52 (CCPA 1981). Since the specification provides no guidance regarding what sort of agents should be screened for inhibiting the processing of amyloid precursor protein, the skilled artisan must resort to trial and error experimentation to determine which class of compounds might yield one with the desired activity. Such trial and error experimentation is considered undue. The skilled artisan must also resort to trial and error experimentation to determine the optimal dosage, duration, and mode of administration of all possible agents. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed."

(iv) Finally, Applicant asserts that the skilled artisan, upon reading Brinton et al. and Roses et al., would have little understanding of the state of the art or the predictability of inhibiting the processing of amyloid precursor protein into amloid beta peptides found in neuritic plaques and

vascular deposits that accumulate in the brains of patients with Alzheimer's disease. Applicant's arguments have been fully considered but are not found to be persuasive. The first step of claim 4 is identifying an agent that decreases the processing of amyloid precursor protein into amyloid beta peptides and the second is step is actually administering this agent to patients with Alzheimer's disease (AD) to inhibit the processing of amyloid precursor protein into amyloid β peptides found in neuritic plaques and vascular deposits that accumulate in the brain. Therefore, claim 4 reads upon administering an agent to an AD patient. Brinton et al. and Roses are pertinent references since they comment on the status of AD treatment at the time the application was filed. Although neither reference discusses inhibition of the processing of amyloid precursor protein into amloid beta peptides *in vivo*, they indicate examples of challenges that may be encountered when administering a possible therapeutic drug to a patient with Alzheimer's disease.

Proper analysis was provided in the previous Office Actions. Due to the large quantity of experimentation necessary to identify an agent that decreases processing of amyloid precursor protein and to determine the optimal dosage, duration, and mode of administration of all possible agents to a patient, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art, and the unpredictability of the effects of inhibiting the processing of amyloid precursor protein into amyloid β plaques *in vivo*, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

2. Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 4 is directed to a method of inhibiting the processing of amyloid precursor protein into amyloid β peptides found in neuritic plaques and vascular deposits that accumulate in the brains of patients with Alzheimer's disease comprising administering to a patient an agent which decreases processing of amyloid precursor protein into amyloid β peptides wherein said agent is identified by (i) contacting NTN2 cells with the agent and (ii) measuring levels of amyloid β peptides formed in the endoplasmic reticulum (ER) of the cells.

The specification teaches that BFA is a pharmacological agent that causes a redistribution of the Golgi into the ER (pg 9, lines 4-6). The specification also discloses that BFA abolishes secretion of Aβ into the medium and reduces overall expression of intracellular Aβ by approximately 60%. The specification also teaches that it was the complete loss of $A\beta_{40}$ that accounts for this decrease and $A\beta_{42}$ is largely unaffected by BFA treatment (pg 8, lines 32-37 through pg 9). However, the specification does not teach any specific agents *that decrease processing of amyloid precursor protein (APP)* into amyloid β peptides found in neuritic plaques and vascular deposits. There is no adequate written description of an entire genus of agents.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

The skilled artisan cannot envision the agent of the encompassed method, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The agent itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

Therefore, only a specific agent, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion

Claim 4 is not allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure: (Post-filing date references by the inventors)

*Phiel et al. Nature 423 : 435-439, 2003. (lithium blocks production of Aβ peptides by interfering with APP cleavage)

Wilson et al. J Neurosci Res 74 : 361-369, 2003. (presenilin/secretases)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BEB
Art Unit 1647
20 April 2004

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER